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The First Synthesis of Vancomycinic Acid

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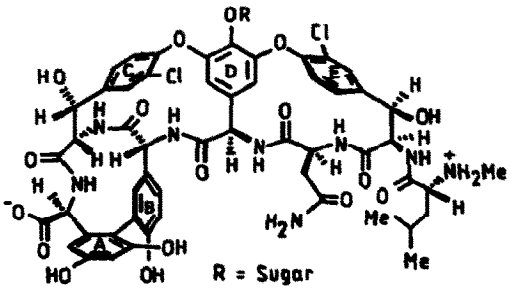
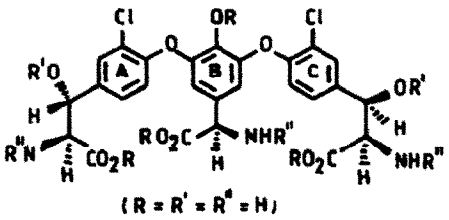
Abstract : Vancomycinic Acid moiety (C, D and E rings) **2** of vancomycin is synthesised making efficient use of the ease of nucleophilic displacements of halides on 2,6-dibromobenzoquinone followed by a diastereoselective elaboration of the quinone unit to aryl glycine.

Vancomycin (1)[1], the most sought after member of the Vancomycin - Ristocetin family of glycopeptide antibiotics (or dalbaheptides) is a human anti-infective agent routinely used against staphylococcal infections. It expresses its antibiotic activity by inhibiting bacterial cell wall biosynthesis by selectively binding to the C-terminal-D-Ala-D-Ala residues of peptido glycan precursor muramyl pentapeptide[2]. Bis-diaryl ether cross linked amino acid fragment (2) constitutes part of the active center of the antibiotic. Vancomycinic acid was obtained as a degradation product of vancomycin.



Vancomycin : 1



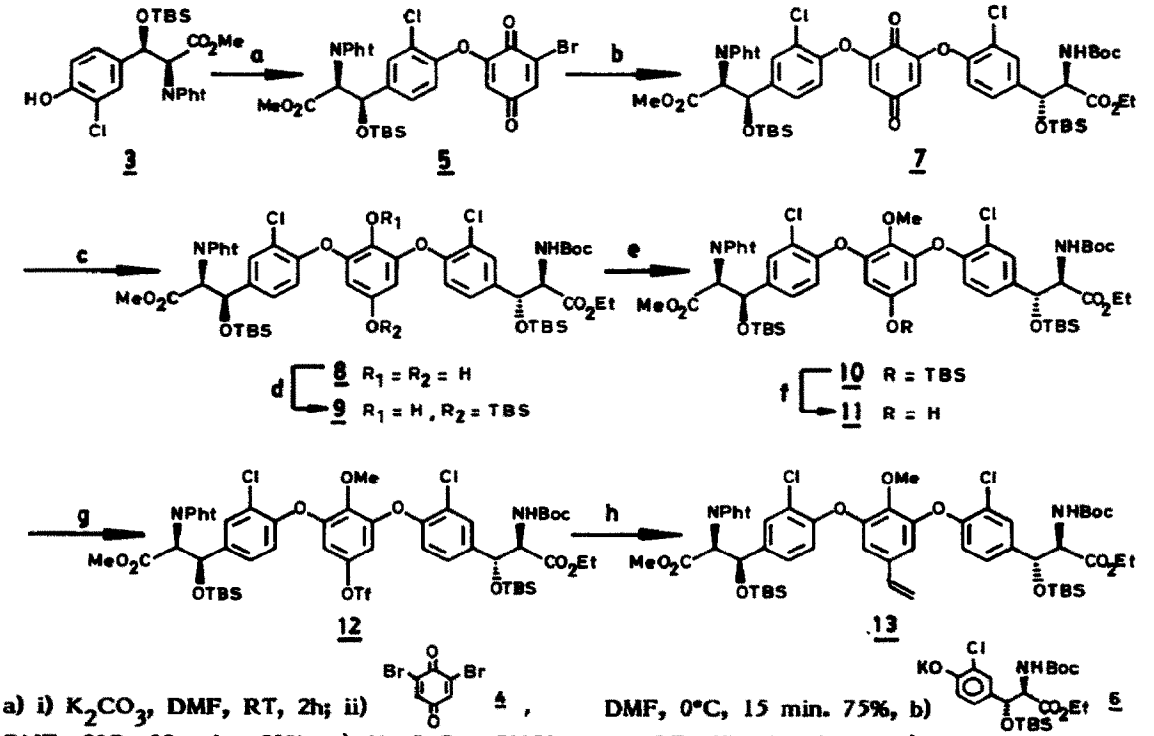
Vancomycinic acid : 2

One of the hurdles in the total synthesis of vancomycin is the efficient buildup of the bis-diaryl ether subunit. Ullmann reaction[3], the classical and most widely used method which requires harsh conditions and is not compatible with amino acids containing base- or heat-sensitive functionalities. Hamilton et al.[4] adopted a method involving displacement by phenolate (or phenoxide) of a tosylate from an activated dinitro aryl compound. Yamamura and Evans group[5] applied the TTN promoted bi-aryl ether cyclisation. The modalities of this approach, where ortho positions of the phenoxide units are substituted by halogen or alkyl groups to control oxidative potential and regioselectivities may not be suitable for vancomycin, because of the difficulty in selective removal of one chlorine atom from each of the aryl amino acid of the bicyclo C, D and E diphenyl ether segment.

In this communication, we report the first synthesis of bis-diaryl ether crosslinked amino acid fragment 2, vancomycinic acid (C, D and E rings) of vancomycin, taking advantage of our recent approach[6] for the synthesis of diphenyl ether cross-linked amino acid by displacement reaction of 2,6-dibromobenzoquinone with suitably substituted phenoxides in order to obtain 2,6-diaryloxy benzoquinone. After linking the two ether units in a sequential fashion, the central benzoquinone unit was elaborated to the corresponding aryl-glycine using the Pd-catalysed vinylation of aryltriflate[7] followed by asymmetric dihydroxylation to generate the required chirality.

Accordingly, 2,6-dibromobenzoquinone[8] (4) was first treated with (2S,3R)-methyl 2-phthalimido-3-(^{t}butyldimethylsilyloxy)-3-(3'-chloro-4'-hydroxy phenyl)propionate[9] (3) in DMF at 0°C using K_2CO_3 as base to get the mono-ether 5 in 75% yield which was then reacted with (2R,3R)-ethyl 2-(^{t}butoxycarbonyl)amino-3-(^{t}butyldimethylsiloxy)-3-(3'-chloro-4'-hydroxy phenyl)propionate[9] (6) under identical conditions to obtain the bis-aryloxy quinone (7) in 53% yield. After reduction of the quinone 7 to the corresponding hydroquinone 8 ($Na_2S_2O_4$, $CHCl_3$-H_2O, r.t, 0.5 h) differential protection of the two phenolic hydroxyls in 8 was carried out by first converting the

SCHEME - I

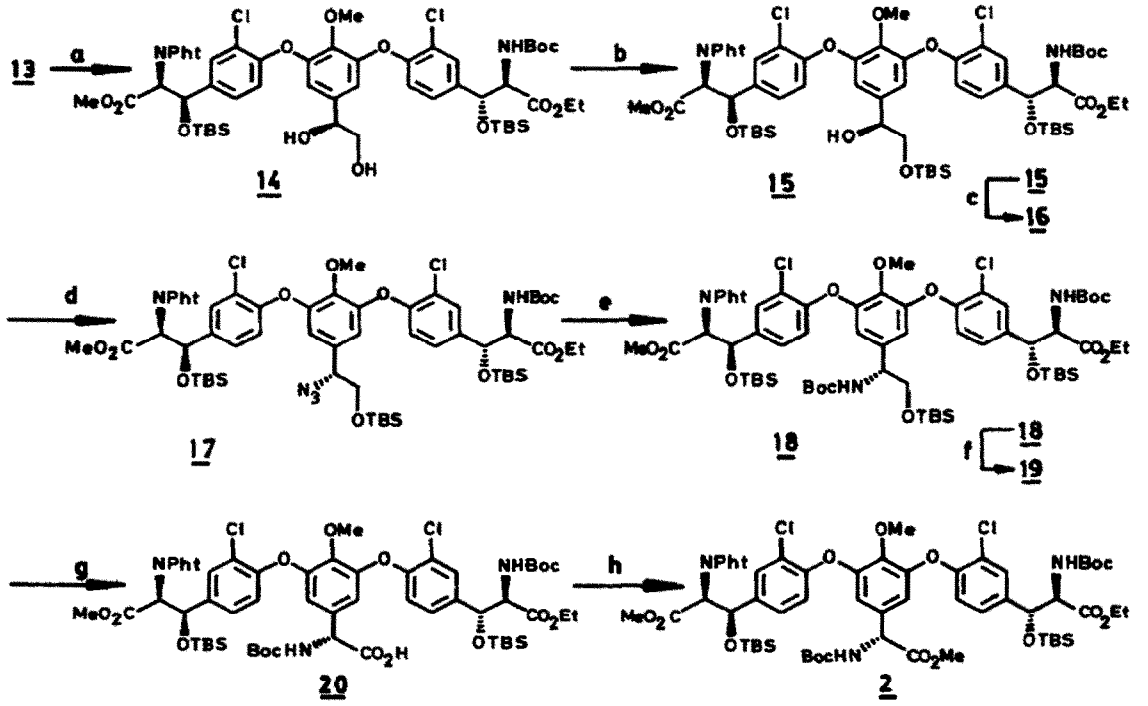


a) i) K_2CO_3, DMF, RT, 2h; ii) 4, DMF, 0°C, 15 min. 75%, b) 6 DMF, 0°C, 30 min. 53%; c) $Na_2S_2O_4$, $CHCl_3$-H_2O, RT, 30 min, 100%; d) TBDMS-Cl, Et_3N, CH_2Cl_2, RT, 2h, 80%; e) DMS, K_2CO_3, Acetone, 50°C, 2h, 90%; f) TBAF (0.5 eq), THF, 0°C, 10 min. 80%; g) Tf_2O, Pyridine, $CH2Cl_2$, 0°C, 30 min, 85%; h) Vinyltributyltin, LiCl, $Pd(Ph_3P)_4$, 2,6-di-t-butyl-4-methylphenol (cat.) Dioxane, 90°C, 1h, 85%.

sterically more accessible phenolic group to its silyl ether (TBDMS-Cl, TEA, CH_2Cl_2, RT, 2 h) followed by O-methylation (DMS, K_2CO_3, acetone, 50°C, 2h) of the resulting silyl ether **9** to give **10** (Scheme I).

We were then confronted with the delicate task of desilylating selectively the phenolic silyl ether in the presence of the two benzylic ones. Surprisingly this could be achieved simply by treating the tri-O-silyl compound **10** with TBAF (0.5 eq)[10] in THF at 0°C to afford **11**. The now free phenolic hydroxyl was converted to its triflate **12** (Tf_2O, Py, CH_2Cl_2, 0°C, 0.5 h) and was transformed smoothly to the styrene **13** (vinyl $SnBu_3$, $Pd(PPh_3)_4$, LiCl, dioxane, 90°C, 1 h) following Stille's procedure[7]. The catalytic asymmetric dihydroxylation (AD)[11] (OsO_4, $K_3Fe(CN)_6$, K_2CO_3, DHQ-9-phenanthryl ether ($^tBuOH:H_2O$) of **13** afforded the diol **14**, the primary alcohol group of which was converted in to the silyl ether **15** (TBS-Cl, TEA, CH_2Cl_2, RT, 1 h) (Scheme II). The diastereomeric excess (85%) was determined by the ^{19}F-NMR spectrum of the Mosher ester[12].

SCHEME - II



a) Dihydroquinine-9-O-phenanthryl ether, OsO_4, K_2CO_3, $K_3Fe(CN)_6$, $^tBuOH:H_2O$ (1:1) RT, 30 h, 90%; b) TBDMS-Cl , Et_3N, CH_2Cl_2, RT, 1h, 75%; c) MsCl, Et_3N, CH_2Cl_2, RT, 2h, 90%; d) NaN_3, DMF, 50°C, 1h, 65%; e) PtO_2-H_2, $(Boc)_2O$, EtOAc, RT, 14h, 70%; f) TBAF (0.5 eq), THF, 0°C, 30 min, 65%; g) PDC, DMF, RT, 10 h, 60%; h) CH_2N_2, Ether, 0°C, 5 min, 70%.

Treatment of **15** with mesyl chloride (Et_3N, CH_2Cl_2, RT, 2h) followed by nucleophilic displacement reaction with NaN_3 (DMF, 50°C, 1h) gave the azido derivative **17**. Reduction

of the azido group in **17** to the amine with concomittant N-Boc protection was carried out in one-pot using PtO_2-H_2 in the presencce of $(Boc)_2O$ to get **18**[13] (70%). Selective primary desilylation (TBAF, DMF, 0°C, 0.5 h) followed by oxidation with PDC in DMF furnished the acid **20** which was esterified with CH_2N_2 to get the CDE fragment **2**.

We have demonstrated in these three communications, that the vital structural units of vancomycin - β -hydroxy-α-amino acids, biaryl and biaryl ether units - can be synthesised by simple and efficient approaches. Total synthesis of vancomycin making use of these methodologies is in progress.

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